# Neuroimmune circuits in inter-organ communication

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Abstract | Studies in recent years have uncovered the crucial function of neuroimmune interactions in maintaining tissue homeostasis and protection. Immune and neuronal cells are often colocalized at defined anatomical sites, forming neuroimmune cell units, where both cell types coordinate their responses. In addition, even when located at distant sites, neuronal cells can receive signals from and provide signals to peripheral immune cells. As such, neuroimmune interactions are found across multiple organs and have recently emerged as important regulators of physiology. In this Review, we focus on the impact of bidirectional neuroimmune interactions in tissue biology, organ physiology and embryonic development. Finally, we explore how this fast-evolving field is redefining the tenets of inter-organ and intergenerational communications.

Substance P
A neuropeptide of 11 amino acids in length belonging to the tachykinin family, formed by differential splicing of the preprotachykinin A gene (*TAC1*). Substance P is widely distributed throughout the nervous system but has been best appreciated as an important neurotransmitter in nociceptive pathways.

In addition to their well-established roles in protective immunity, immune cells can also sense environmental cues in the absence of infection. Notably, discrete immune cell subsets have been shown to integrate dietary, metabolic and unrelated tissue cues to promote intra-organ and inter-organ communication and homeostasis[1,2]. A clear example of these immune sensing strategies is provided by the reciprocal communication between neuronal and immune cells in health and disease. We have known about the importance of neuroimmune interactions for decades[3,4], with most research focusing on how stress-related cues influence immune responses and how immune cytokines impact brain activity and behaviour[5,6]. However, more recently, studies have revealed that neuronal and immune cells can colocalize and productively interact in peripheral-tissue-specific neuroimmune cell units[7], forming local circuits that control tissue defence and homeostasis[2,8–10]. Neuroimmune interactions have also been described in several pathological conditions, including autism, cancer, multiple sclerosis and chronic inflammatory disorders[8,10,11]. Herein, we review recent findings on the impact of bidirectional neuroimmune interactions within major body organs, such as the skin, lungs and intestines, and we explore how the communication between the neuronal and immune systems underlies communication between organs, notably between the gut and the brain, in health and disease.

## Neuroimmune interactions in the skin

The skin contains an extensive network of immune and neuronal cells that are important for its barrier function[12]. Moreover, recent studies have demonstrated that reciprocal neuroimmune interactions contribute to the pathogenesis of several dermatological conditions[8].

Various immune cell subsets present in the skin can regulate the function and regeneration of skin neurons. For example, the T cell-derived cytokine IL-4 can induce chronic itch via sensory neuron activation in the skin[13]. Notably, chronic itch was shown to rely on neuronal signalling through IL-4 receptor-α (IL-4Rα) and Janus kinase 1 (JAK1), and patients with chronic itch that was unresponsive to standard immunosuppressive therapies responded positively to treatment with JAK inhibitors[13]. Similarly, mast cell–neuronal interactions were also shown to contribute to pain and itch, as has been reviewed in full elsewhere[14]. For example, house dust mites activate nociceptor neurons that in turn drive the development of allergic skin inflammation by inducing the degranulation of mast cells via substance P, which activates mast cells through the mast cell-specific receptor MAS-related G protein-coupled receptor member B2 (MRGPRB2)[15]. Finally, a subset of macrophages that seed the skin prenatally were shown to interact with local sensory nerves and trim their myelin sheath, which contributes to axon sprouting and nerve regeneration after mechanical injury of the skin[16].

Multiple studies have demonstrated intercellular communication in the other direction, with neuron-derived signals regulating dermal immune cells. A clear example is provided by the effects of nociceptor neurons on skin neutrophils. Nociceptor-derived calcitonin gene-related peptide (CGRP), a vasodilator neuropeptide also involved in nociception, was shown to inhibit neutrophil recruitment and opsonophagocytic activity during *Streptococcus pyogenes* necrotizing infection in the skin[17]. *S. pyogenes* directly activates transient receptor potential cation channel V1 (TRPV1)-positive nociceptor neurons through secretion of the pore-forming toxin streptolysin S. In turn, nociceptor neuronal activation triggers the release

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https://doi.org/10.1038/s41577-019-0247-z

Nociceptor neurons
Sensory neurons that are activated by noxious or damaging stimuli. Nociceptor neurons are classified according to their ability to respond to mechanical, thermal and chemical stimuli. Free nerve endings in the periphery serving as receptive sites extend from neuronal cell bodies in the dorsal root or cranial nerve ganglia.

Nociception
The neural process of encoding noxious mechanical, thermal and/or chemical stimuli that occurs in afferent fibres, which send signals to the central nervous system.

Cholinergic neurons
Neuronal cells that mostly communicate via the neurotransmitter acetylcholine.

Dorsal root ganglia
The cell bodies of sensory neurons are collected together in paired ganglia that lie alongside the spinal cord. These neurons are pseudo-unipolar in nature, meaning that they have one axon with two processes: one peripheral axonal branch that innervates the tissues of the body to receive sensory information and one axonal branch that sends nerve impulses to the spinal cord. Dorsal root ganglia also contain satellite glia and macrophages that can modulate the function of sensory neurons.

of neuron-derived CGRP that inhibits neutrophil recruitment[17] (TABLE 1). Similarly, TRPV1$^+$ nociceptor sensory neurons were shown to release CGRP, suppressing pulmonary neutrophil recruitment and activation during *Staphylococcus aureus* infection of the lungs[14]. CGRP antagonists were shown to improve infection outcomes[17,18], suggesting that blocking this pathway may promote host defence against defined bacterial infections (FIG. 1).

Dendritic cells (DCs) in the skin have also been shown to interact with local neurons[19,20]. Skin nociceptor neurons establish close interactions with DCs to regulate γδ T cells via the induction of IL-23, a cytokine that induces cells with an inflammatory gene signature, including IL-17 production[19,20]. Specifically, sensory neurons (defined as $Na_v1.8^+TRPV1^+$) in the skin induce IL-23 production by local DCs, which in turn activate γδ T cells to produce IL-17 and IL-22, thus eliciting the IL-23–IL-17 pathway in the context of fungal infection and psoriasiform skin inflammation. γδ T cell activation then leads to increased recruitment of inflammatory neutrophils and monocytes to the skin[20]. Similarly, in the setting of cutaneous candidiasis (protection against which depends on a rapid IL-17-mediated immune response), sensory neurons directly sense *Candida albicans* and promote infection control via CGRP[19]. Notably, *C. albicans*-induced CGRP promoted the production of IL-23 by dermal DCs that elicited IL-17 production from local γδ T cells[19] (FIG. 1).

Together, these studies indicate that dermal neuroimmune interactions may be interesting candidates to be harnessed therapeutically in the future. Nevertheless, further studies will be required to elucidate the efficiency and specificity of such approaches in the therapy of skin disorders.

## Neuroimmune interactions in the airways

The airways are frequently home to allergic reactions that are accompanied by hyper-reactivity of the airways, cough, spasm and inflammation[21–23]. These manifestations indicate that allergy associates with impaired airway innervation and dysregulated immune responses, suggesting that neuronal and immune responses may synergize and crosstalk to regulate allergic responses in the lungs[24]. Supporting this idea, neurons and inflammatory cells have been found in close proximity in the airways[25,26]. For example, following allergen exposure, mast cells and eosinophils cluster and surround neuronal cells in the lungs[27–31], and local neurons cooperate with mast cells to cause bronchoconstriction[30]. Pulmonary neurons express intercellular adhesion molecule 1 (ICAM1) and CC-chemokine ligand 11 (CCL11) that control eosinophil recruitment[32–34]. In addition, neuronal-derived vasoactive intestinal peptide (VIP) and substance P induce mast cell-derived histamine, leukotriene $C_4$, prostaglandin $D_2$, IL-6 and tumour necrosis factor (TNF), which together contribute to the triggering of allergic type 2 immune reactions[30,35,36].

Group 2 innate lymphoid cells (ILC2s) in the lungs were recently shown to interact with pulmonary neurons[8]. Notably, ILC2s express VIP receptor 2 (VIPR2) and activation of this receptor induces IL-5 secretion and eosinophilia[37]. Reciprocally, IL-5 signals back to lung nociceptors promoting VIP secretion, thus further activating ILC2s (REF.[38]). Interestingly, this positive feedback loop can be terminated by pharmacological silencing of pulmonary sensory neurons, suggesting that blocking these neuronal–ILC2 interactions may be a therapeutic option in the context of allergy[38] (FIG. 2). Pulmonary cholinergic neurons also regulate innate type 2 responses via neuromedin U (NMU)[39–41]. ILC2s selectively express NMU receptor 1 (*Nmur1*), the gene encoding a peripheral receptor of NMU[39–41], and pulmonary ILC2s are found in the vicinity of NMU-expressing cholinergic neurons[39–41]. NMU induces lung ILC2 proliferation and a uniquely potent production of innate IL-5, IL-13 and amphiregulin[39–41]. As such, NMU-induced ILC2 activation triggers the increase of pulmonary mast cell and eosinophils, thus contributing to improved antihelminth responses in the lungs[39–41] (FIG. 2). Interestingly, IL-13 was also shown to increase *Nmu* expression in dorsal root ganglia neurons, thus suggesting the existence of a reciprocal neuron–ILC2 regulatory loop via ILC2-derived IL-13 and neuronal NMU expression[41]. Cholinergic neurons were also shown to modulate α7-nicotinic acetylcholine receptor (α7nAChR)-expressing ILC2s[42]. Notably, activation of α7nAChR on ILC2s leads to impaired innate cytokine production and reduced airway hyper-responsiveness[42]. These studies demonstrate that pulmonary neuronal–ILC2 units can trigger immediate tissue protection via a rapid neuroimmune programme that acts as a rheostat of ILC2 responses, which is in contrast to the comparatively slower kinetics of the regular cytokine-mediated and alarmin-induced ILC2 activation.

Pulmonary neuroendocrine cells (PNECs) are also present in the vicinity of pulmonary ILC2s and peptidergic neurons[43], and PNECs secrete γ-aminobutyric acid (GABA) under the control of a neurotrophin 4-dependent neural circuitry that is established during development[44]. Interestingly, PNECs regulate goblet cell

Table 1 | **Neuroimmune interactions in peripheral tissues**

| Neural cell type | Immune cell type | Organ | Refs |
|---|---|---|---|
| Nociceptor TRPV1$^+$ sensory neurons | Neutrophils | Skin | 17 |
| Nociceptor TRPV1$^+$ sensory neurons | Neutrophils | Lung | 18 |
| Vagus nerve; cholinergic neurons | Muscularis macrophages | Intestine | 54 |
| Enteric neurons | Muscularis macrophages | Intestine | 72 |
| Extrinsic sympathetic neurons | Muscularis macrophages | Intestine | 71 |
| Sympathetic neurons | Macrophages | Adipose tissue | 73 |
| Nociceptor sensory neurons | ILC2s | Lung | 38 |
| Pulmonary neuroendocrine cells | ILC2s | Lung | 43 |
| Cholinergic neurons | ILC2s | Lung and intestine | 39–41 |
| Adrenergic neurons | ILC2s | Intestine | 83 |
| Glial cells | ILC3s | Intestine | 75 |
| Nociceptor $Na_v1.8^+TRPV1^+$ neurons | Dendritic cells | Skin | 19,20 |

ILC, innate lymphoid cell; TRPV1, transient receptor potential cation channel V1.

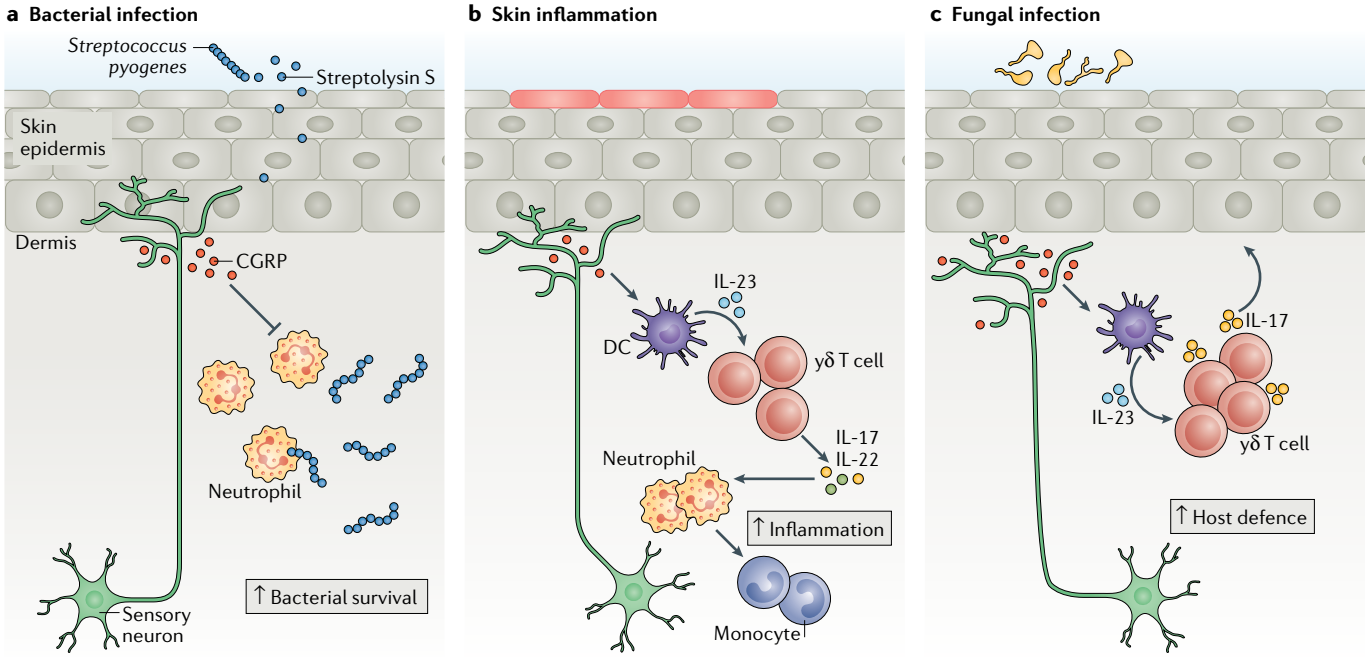


Fig. 1 | **Neuroimmune crosstalk in the skin. a** | Dermal sensory neurons are activated by *Streptococcus pyogenes*-derived streptolysin S toxin and release calcitonin gene-related peptide (CGRP), which suppresses the recruitment and activity of peripheral neutrophils. **b**, **c** | Dermal dendritic cells (DCs) are regulated by sensory neuron-derived CGRP during skin inflammation and infection with the fungal organism *Candida albicans*. Nociceptor neurons (which express $Na_v1.8$ and transient receptor potential cation channel V1 (TRPV1)) induce DC-derived IL-23 production, which then activates γδ T cells to produce IL-17 and IL-22.

hyperplasia and ILC2s via GABA and CGRP production, respectively[43] (FIG. 2). More recently, several studies indicate that CGRP may act as a context-dependent negative regulatory factor shaping ILC2 responses to alarmins and neuropeptides[45–47]. Thus, PNEC–ILC2 units may form important allergy-modulating units in the lungs. Accordingly, lungs from human asthmatic patients show increased PNECs[43].

Finally, similarly to dermal DCs, pulmonary DCs are located in proximity of CGRP-expressing nociceptors[48–51] and nociceptor neuron-derived CGRP was shown to inhibit γδ T cell and neutrophil responses in the context of bacterial pneumonia[17,18] (FIG. 2). Taken together, these studies indicate that neuroimmune cell units have important roles in the pathogenesis of lung disease. Nevertheless, we still need a better understanding of neuroimmune circuit architecture and of the mechanisms underlying neuroimmune interactions.

## Neuroimmune interactions in the intestine

The intestine contains the largest amount of lymphoid tissue in the body and has an extensive nervous system that ensures intestinal homeostasis and function. The intestine receives extrinsic (sympathetic and parasympathetic) and intrinsic (enteric nervous system) neuronal signals[8]. Neurons of the enteric nervous system have their cell bodies within the walls of the intestine, and are organized into the myenteric plexus and the submucosal plexus, forming two layers of interconnected ganglia[52]. Importantly, submucosal neurons control gut secretions, nutrient absorption and gut blood flow, whereas myenteric plexus neurons regulate smooth muscle contractions[53,54]. The diversity of neuronal and immune cell types in the gut allows for tailor-made responses to distinct challenges[55] (TABLE 1). Importantly, intestinal immune and neuronal cells have been implicated in bidirectional neuroimmune circuits that regulate fundamental aspects of enteric physiology, including gut secretion, peristalsis and enteric defence. This crosstalk is mostly based on the expression of neurotransmitter and neuropeptide receptors in immune cell subsets and the expression of cytokine receptors in neuronal cells[8,10,56], suggesting that coordinated enteric neuroimmune responses are important pillars of intestinal physiology.

Multiple innate immune cell subsets productively interact with enteric neuronal cells. For example, mast cells interact with enteric neurons in their close vicinity[4,57,58]. On the one hand, mast cell-derived histamine and tryptase activate myenteric and submucosal neurons, respectively[59–61]. On the other hand, peptidergic neurons regulate mast cells via production of substance P, CGRP and VIP[36,57,62]. Interestingly, mast cell proteases were also shown to cleave neuronal substance P and VIP[63], indicating that mast cells can limit neuronal activation[57]. Together, these findings indicate that enteric mast cells and neurons form bidirectional circuits that may be important in the context of intestinal conditions. For example, colonic biopsies from patients with irritable bowel syndrome were shown to have high levels of histamine and tryptase[64–66], correlating with increased mast cells in the vicinity of enteric neurons from these patients[64,65]. Interestingly, patients with inflammatory bowel disease have altered sympathetic innervation[67], and inflammation impacts sympathetic nerves by

Pulmonary neuroendocrine cells
(PNECs). Specialized epithelial cells that are present in the airways. Neuroendocrine cells can be found as solitary cells or associated in cell clusters called pulmonary neuroepithelial bodies. Neuroendocrine cells receive neuronal input that controls the release of endocrine molecules.

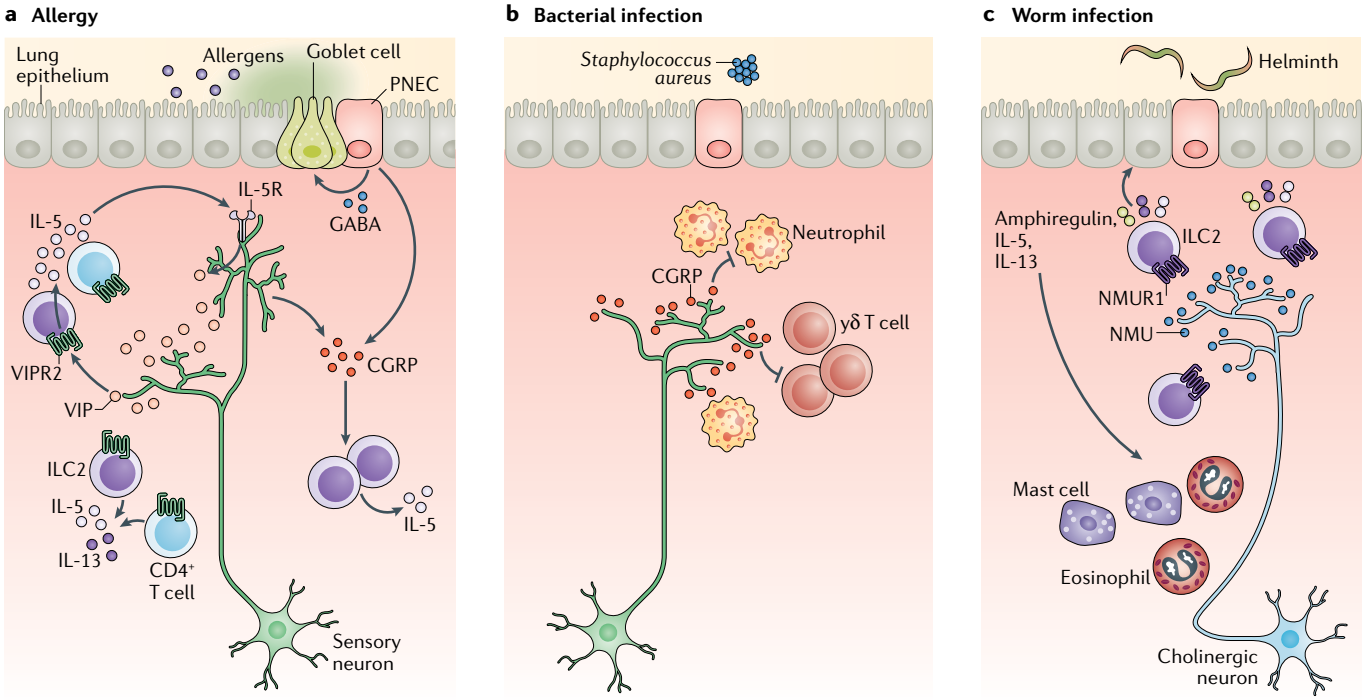


Fig. 2 | **Neuroimmune crosstalk in the lungs. a** | Neuron-derived vasoactive intestinal peptide (VIP) binds to VIP receptor 2 (VIPR2) expressed by group 2 innate lymphoid cells (ILC2s) and increases their production of IL-5. In turn, IL-5 stimulates nociceptors to produce more VIP, generating a type 2 loop that potentiates allergy. Pulmonary sensory neurons also control ILC2s through the release of calcitonin gene-related peptide (CGRP), which induces IL-5 production. **b** | CGRP suppresses pulmonary neutrophil recruitment and γδ T cell-mediated defence during *Staphylococcus aureus* infection. **c** | In response to helminth infection, pulmonary cholinergic neurons release neuromedin U (NMU), which binds to NMU receptor 1 (NMUR1) on ILC2s, which promote protective responses through the release of type 2 cytokines. GABA, γ-aminobutyric acid; IL-5R, IL-5 receptor; PNEC, pulmonary neuroendocrine cell.

inducing the sprouting of sensory neurons, which contributes to visceral hypersensitivity in inflammatory bowel diseases[68,69].

Intestinal macrophages, which are mostly located in the lamina propria and in the muscularis[70], also interact with enteric neurons in a bidirectional manner[71,72]. Muscularis macrophages contribute to motility of the gastrointestinal tract. Accordingly, colony stimulatory factor 1 receptor (CSF1R)-deficient mice, which lack muscularis macrophages, display dysfunctional intestinal motility[72]. In terms of the mechanism, bone morphogenetic protein 2 (BMP2) produced by muscularis macrophages controls peristalsis via activation of BMP receptor (BMPR) expressed by enteric neurons; administration of BMPR inhibitors leads to altered peristalsis; and BMP2 administration restores peristalsis[72]. Reciprocally, intestinal neurons are a main source of CSF1 downstream of signals from commensal microorganisms, by an as yet unidentified microbial sensing mechanism[72]. Interestingly, stimulation of the vagus nerve was shown to regulate intestinal muscularis macrophages via the acetylcholine–α7nAChR anti-inflammatory pathway[54]. In agreement, α7nAChR activation negatively regulates ATP-induced calcium responses in intestinal macrophages[54].

During infection with *Salmonella typhimurium*, extrinsic sympathetic neurons in the gut muscularis become activated and release noradrenaline, which acts on muscularis macrophages that express β2 adrenergic receptor (β2AR)[71]. Importantly, noradrenaline-mediated activation of these β2AR-expressing macrophages drives a tissue-protective macrophage phenotype, notably by the induction of *Arg1* and *Chi3l3* expression, that may be important to preserve an anti-inflammatory milieu in the muscularis[71]. Together, these findings indicate the existence of enteric bidirectional neuron–macrophage cell units orchestrated by microbial signals (FIG. 3). Although functional neuron–macrophage cell units have been described in the intestine and the skin, it is not clear whether such interactions exist in other organs where these cell types are abundant. Nevertheless, macrophages in the adipose tissue were also shown to integrate neuron-derived cues[73], suggesting that neuron–macrophage cell units might have a broader anatomical distribution, contributing to fine-tuned tissue and organ homeostasis.

ILCs are abundant at the mucosal enteric barrier and have been reported to actively interact with neuronal cells, as ILC2s do in the lungs[9,74]. For example, enteric glial cells control intestinal ILC3s[75]. Specifically, enteric ILC3s in the adult mouse intestine express the neuroregulator tyrosine kinase receptor RET and mice with RET-deficient ILC3s have impaired IL-22 production, reduced epithelial reactivity and increased susceptibility to *Citrobacter rodentium* infection[75]. Enteric glial cells, which are major producers of RET-activating neurotrophic factors, such as glial-derived neurotrophic factor family ligands (GFLs), closely colocalize with ILC3s.

Vagus nerve
The nerve that connects the brainstem to the rest of the body. It contributes to the autonomic nervous system, which consists of the parasympathetic and sympathetic arms.

Enteric glial cells
A type of peripheral glia that are similar to astrocytes of the central nervous system. Among other functions, they maintain the structural integrity of the nervous system, provide trophic support to neurons, insulate one neuron from another and can clear debris.

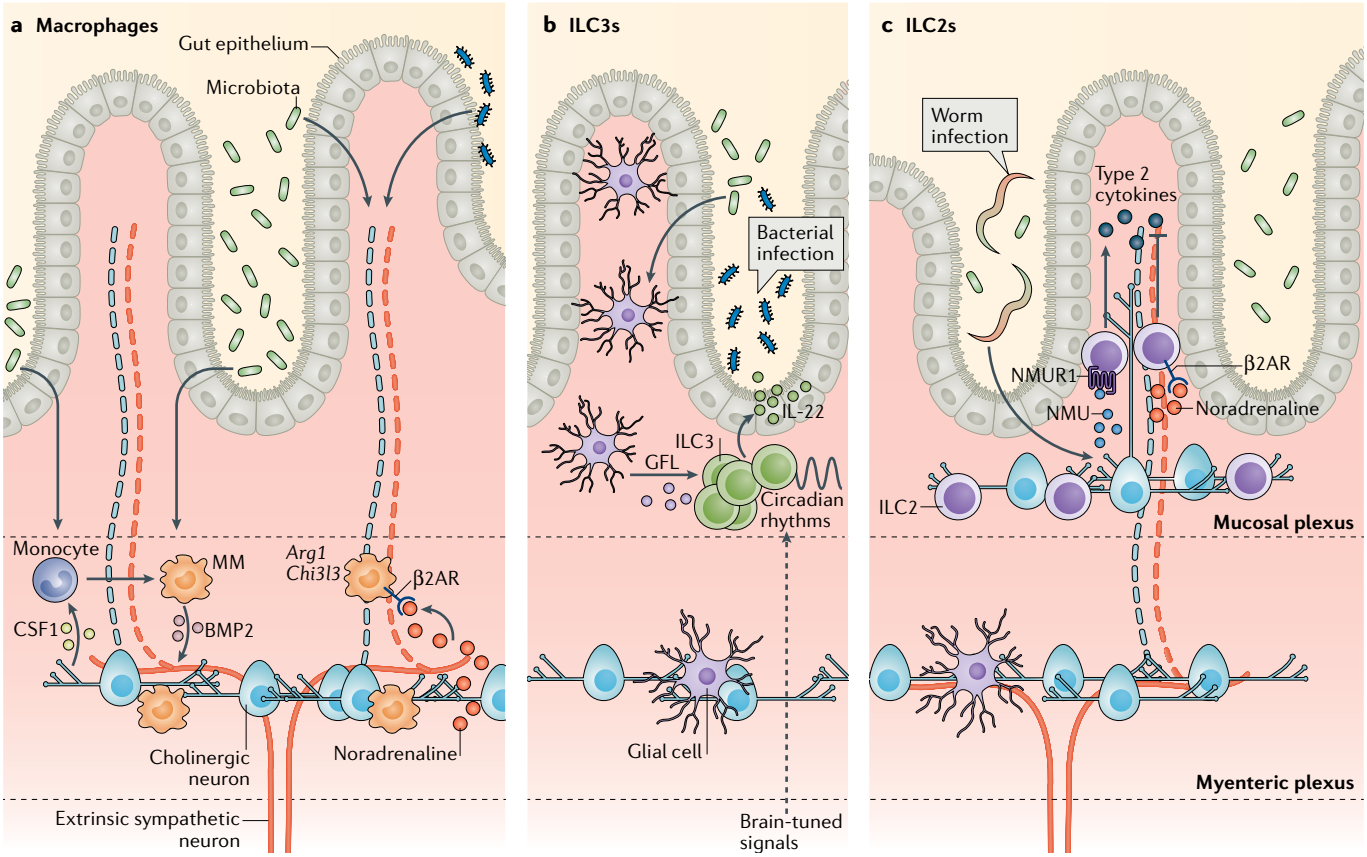


Fig. 3 | **Neuroimmune crosstalk in the gut. a** | Interactions between colony stimulatory factor 1 (CSF1)-producing enteric neurons and bone morphogenetic protein 2 (BMP2)-producing muscularis macrophages (MMs) are modulated by the microbiota. Activation of sympathetic neurons by bacterial products induces a tissue-protective phenotype in MMs (indicated by expression of *Arg1* and *Chi3l3*). **b** | Intestinal glial cells sense microbial products, leading to the production of glial-derived neurotrophic factor family ligands (GFLs) that, in turn, activate RET-expressing group 3 innate lymphoid cells (ILC3s) and the production of innate IL-22. Brain-tuned circadian circuits regulate intestinal ILC3 homeostasis. **c** | Cholinergic neurons directly sense helminth-derived products and increase neuromedin U (NMU) expression. NMU activates ILC2s through the NMU receptor 1 (NMUR1) and induces the production of innate type 2 cytokines. By contrast, local noradrenaline inhibits ILC2s that express β2 adrenergic receptor (β2AR).

Microbial products sensed in a myeloid differentiation primary response 88 (MYD88)-dependent manner by glial cells drive their production of GFLs[75]. Thus, enteric glial cells translate microbial cues into neurotrophic factor production that controls ILC3 and intestinal homeostasis (FIG. 3). Interestingly, RET signals were also shown to modulate haematopoietic cell functions and Peyer's patch development[76–78], suggesting that this neuroregulatory axis may be more broadly operational in other immune cell subsets. In addition to enteric glial cells, vagus nerve-derived signals were also shown to regulate ILC3 responses to bacterial infections in the peritoneal cavity, notably via acetylcholine-induced upregulation of the biosynthetic pathway for pro-resolving protectins in ILC3s (REF.[79]). In agreement, administration of the protectin conjugate PCTR1 or ILC3s to vagotomized mice restored host responses to bacterial infection[79]. Finally, it was recently shown that enteric ILC3s can integrate light-entrained and brain-tuned circadian signals to regulate intestinal homeostasis[80]. ILC3-intrinsic circadian dysregulation led to disrupted gut ILC3 homeostasis[80–82], impaired epithelial reactivity, dysregulated microbiome, increased susceptibility to bowel infection and disrupted lipid metabolism[80]. Interestingly, dysregulation of brain rhythmicity led to disrupted circadian ILC3 oscillations, dysregulated microbiome and altered lipid metabolism, indicating that systemic circadian neuroimmune circuits regulate enteric ILC3 function and intestinal homeostasis[80].

As described earlier in the lungs, ILC2s can integrate neuron-derived signals to promote tissue homeostasis and defence[9]. Intestinal cholinergic neurons were shown to directly regulate local innate type 2 responses via NMU[39–41]. ILC2s colocalize with enteric NMU-expressing cholinergic neurons[39,40], and NMU induces fast and potent innate type 2 responses, notably the production of IL-5, IL-13 and amphiregulin[39,40]. As such, infection with the parasite *Nippostrongylus brasiliensis* induces upregulation of enteric *Nmu* expression, and administration of NMU during infection results in increased innate type 2 responses and reduced tissue damage and *N. brasiliensis* infection burden[39,40]. Interestingly, *N. brasiliensis* excretory–secretory products induce *Nmu* expression by cholinergic neurons

Table 2 | **Neuroimmune interactions in the gut–brain axis**

| Inducer | Messenger | Target (outcome) | Refs |
|---|---|---|---|
| Short-chain fatty acids | $T_{reg}$ cells | Microglia | 82 |
| Long-chain fatty acids | $T_H17$ cells | Brain cells (EAE) | 91 |
| High salt | $T_H17$ cells | Brain cells (EAE) | 95,96 |
| *Lactobacillus reuteri* | $T_{reg}$ cells, IELs | Brain cells (EAE) | 101 |
| Indole-3-lactic acid | $T_H17$ cells | ND | 97 |
| High salt | $T_H17$ cells | Brain (cognitive dysfunction) | 103 |
| Indoxyl-3-sulfate | NA | Microglia, astrocytes | 86,110 |
| Immune cells | IFNγ, TNF, IL-1β, IL-4, IL-13, IL-18, IL-17 | Neurons | 112–119 |
| Segmented filamentous bacteria | $T_H17$ cells | Brain cells (EAE, autism) | 88,89,125 |
| Commensal bacteria | γδ T cells, $T_{reg}$ cells | Brain cells (ischaemia) | 127–130 |
| *Bacteroides fragilis* | IL-10-producing cells | Brain cells (EAE) | 126 |
| ND | B cells | Brain cells (EAE) | 90 |

EAE, experimental autoimmune encephalomyelitis; IEL, intraepithelial lymphocyte; IFNγ, interferon-γ; NA, not applicable; ND, not determined; $T_H17$ cell, T helper 17 cell; TNF, tumour necrosis factor; $T_{reg}$ cell, regulatory T cell.

in a MYD88-dependent manner[39]. In addition to cholinergic neurons, the intestine has an important set of sympathetic catecholaminergic neurons[10]. These sympathetic catecholaminergic neurons produce noradrenaline that signals through β2AR on target cells[10]. ILC2s express β2AR and colocalize with adrenergic neurons[83]. β2AR deficiency leads to increased innate type 2 cytokine production in the intestine and lower helminth infection burden, effects that can be reversed by β2AR agonists[83]. Together, these studies indicate that intestinal ILCs integrate neuronal signals that critically shape their responses to control tissue homeostasis and defence (FIG. 3). Finally, these studies have started to uncover how neuron–ILC units act as immediate fast rheostats, turning on and off neuroimmune responses that control intestinal defence and tissue repair.

Sympathetic catecholaminergic neurons
Sympathetic neurons are normally assumed to be part of the peripheral nervous system, but many of these neuronal cell bodies are present in the central nervous system. Sympathetic neurons of the spinal cord communicate with peripheral sympathetic neurons. In response to this stimulus, postganglionic neurons release catecholamines that bind adrenergic receptors on target cells inducing 'fight-or-flight' responses.

Blood–brain barrier
A physiological barrier between blood vessels and brain parenchyma. The barrier is formed by specialized tight junctions between endothelial cells of the blood vessel wall, which is surrounded by a basement membrane and an additional membrane formed from astrocyte feet and microglial cells, known as the glial limitans.

## The gut–brain axis

The notion that connections between the gut and the brain significantly contribute to wellness in humans is not new. For example, Elie Metchnikoff proposed that beneficial bacteria could delay cognitive decline and improve human health by manipulating the intestinal environment[84]. Lately, advances in high-throughput sequencing technologies enabled the identification of trillions of bacteria leading to the elucidation of many novel interactions between gut-residing bacteria and the host that take place in both health and disease states.

The gut–brain axis mostly refers to afferent (stimulus) and efferent (response) communication routes that exist between these two organs. Herein, we mainly focus on afferent routes despite a small number of studies starting to detail efferent routes. Different afferent routes conduct information flow between the brain and the intestine (TABLE 2). First, bacteria are sensed by the peripheral nervous system such as the enteric and vagus nerves[85], which constitute dedicated physical connections to the brain stems. Second, gut-residing bacteria produce small molecules (or metabolize host-derived or diet-derived products) that can diffuse to the brain and have direct effects on neuronal cells and resident immune cells, such as microglia[86,87]. Although it is not well understood how such metabolites cross the blood–brain barrier and gain access to the brain, we present a few examples of bacterial small-molecule metabolites that act on immune cells in the brain. Third, gut-residing bacteria affect peripheral immune cells that then relay signals to the brain[88–90]. Notably, upon bacteria-induced activation, immune cells secrete soluble factors that reach the brain, modulating its neuronal cell functions. Alternatively, immune cells can migrate from the gut to the brain, where they have neuromodulatory and immunomodulatory actions (FIG. 4). Among these routes of gut–brain communication, we focus on those that show a clear involvement of immune cells.

***Bacterial metabolites and the brain.*** Dietary fatty acids directly impact the differentiation of adaptive immune cells in the gut, contributing to autoimmune pathologies in the central nervous system (CNS)[91]. Specifically, long-chain fatty acids promote the differentiation of inflammatory effector T cells, such as T helper 1 ($T_H1$) cells and IL-17-producing $T_H17$ cells, in the gut and exacerbate experimental autoimmune encephalomyelitis (EAE) phenotypes in mice[91]. By contrast, short-chain fatty acids (SCFAs) mitigate EAE. In humans and mice, SCFAs (including acetic acid, propionic acid and butyric acid) are bacterial metabolites of dietary fibre and function either through binding to their cognate receptors, such as the G protein-coupled receptor pair GRP41 and GPR43 (REF.[92]), or through inhibiting histone deacetylase activity[93]. Although their mechanism of action is still controversial, SCFAs enhance the differentiation of regulatory T ($T_{reg}$) cells that promote anti-inflammatory responses[92–94]. Dietary supplementation of SCFAs also promotes maturation of microglia (the brain-resident macrophages) in germ-free mice. Removal of the SCFA receptor GPR43 (encoded by *Ffar2*) recapitulates immature microglial phenotypes in germ-free or antibiotic-treated animals[87]. It is still unclear, however, how bacterial-produced SCFAs affect microglial maturation. *Ffar2* expression was not detected in microglia or any other CNS cells, suggesting that SCFAs promote microglial maturation through unknown mechanisms in a receptor non-autonomous manner. Unlike GPR43-deficient mice, mice lacking Toll-like receptors (TLRs), such as TLR2, TLR3, TLR4, TLR7 and TLR9, displayed the normal appearance, density, morphology and maturation status of microglia[87]. Thus, microbial-associated molecular patterns such as lipoproteins, double-stranded RNA, lipopolysaccharides and unmethylated CpG oligonucleotides are unlikely to play roles in promoting microglial maturation.

A high-salt diet (HSD) induces $T_H17$ cell responses through the action of the salt-sensing kinase serum glucocorticoid-regulated kinase 1 (SGK1), which promotes IL-23R expression that enhances $T_H17$ cell function and exacerbates EAE phenotypes[95,96]. A HSD also induces changes in the composition of the microbiota, leading to the depletion of *Lactobacillus murinus*[97].

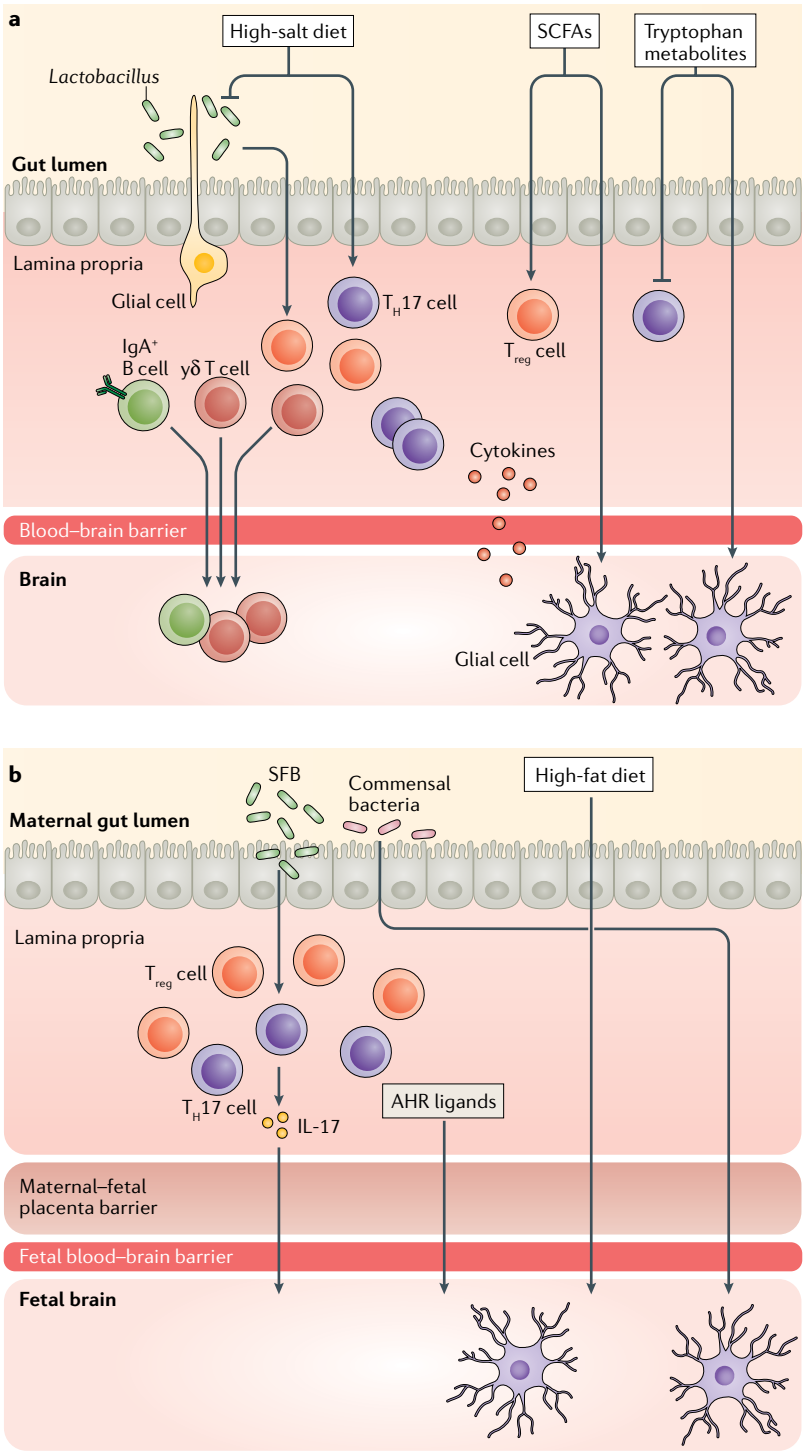


Fig. 4 | **The gut–brain axis and the maternal gut–fetal brain axis.** It is currently unclear how immune cells and effector molecules in the periphery cross the placental and blood–brain barriers to access cells in the brain. **a** | Diet, bacterial metabolites (such as short-chain fatty acids (SCFAs) and tryptophan metabolites), immune cells in the periphery and cytokines have long-range effects on the function and maturation of brain-resident cells. Certain immune cells such as γδ T cells and IgA-producing B cells can migrate into the brain from the intestines. **b** | Changes in the composition of commensal bacteria, a high-fat diet and immune cell activation in pregnant mothers can affect brain development in developing embryos, leading to long-term behavioural changes in the affected offspring. Conversely, increased levels of regulatory T ($T_{reg}$) cells during pregnancy may counteract inflammatory immune cell function and support fetal development. AHR, aryl hydrocarbon receptor; SFB, segmented filamentous bacteria; $T_H17$ cell, T helper 17 cell.

Accordingly, supplementing mice fed a HSD with *L. murinus* or its related human commensal *Lactobacillus reuteri* suppresses the increase in $T_H17$ cells normally associated with a HSD[97]. Previous studies suggest that *L. reuteri* promotes the differentiation of multiple immune cells in the gut, including $T_{reg}$ cells[98] and the immunoregulatory population of $CD4^+CD8\alpha\alpha^+$ intraepithelial lymphocytes[99,100]. Importantly, adoptive transfer of intraepithelial lymphocytes has been shown to ameliorate EAE symptoms[101]. In addition, *L. reuteri* was shown to propagate, presumably due to increased availability of the amino acid tryptophan, in mice deficient in the expression of indoleamine 2,3-dioxygenase 1 (IDO1) and produce indole derivatives including indole-3-aldehyde[102]. Indole-3-lactic acid, the level of which decreases on a HSD, reduces $T_H17$ cell differentiation in a dose-dependent manner when added to in vitro T cell cultures[97]. Therefore, in addition to its direct effects on SGK1, a HSD likely results in increased $T_H17$ cell levels through several mechanisms. First, through decreased $T_{reg}$ cell and intraepithelial lymphocyte numbers due to loss of *Lactobacillus* species; and second, through decreased levels of tryptophan-derived bacterial metabolites that reduce $T_H17$ cell differentiation. In turn, HSD-expanded intestinal $T_H17$ cells lead to a significant increase in plasma IL-17A levels, promoting endothelial dysfunction and cognitive impairment[103]. Using a novel object recognition task to assess memory, wild-type mice on a HSD spent an equal amount of time exploring novel versus familiar objects, indicating a failure to identify the novel one, whereas mice genetically deficient for *Il17a* spent more time with novel objects than familiar objects even when on a HSD, suggesting a role for IL-17A in the cognitive dysfunction associated with HSD[103]. Colonizing mice with *L. reuteri* and other *Lactobacillus* strains corrected various behavioural abnormalities, including social deficits[85,104], anxiety[105] and depression-like[106] symptoms. In line with these findings, *L. reuteri* promotes increased production of oxytocin[107,108], a well-known neuromodulator promoting social behaviours.

Bacteria-produced metabolites modulate the function of the ligand-activated transcription factor aryl hydrocarbon receptor (AHR), which is expressed by both immune and non-immune cells in the brain. Upon ligand binding, AHR translocates from the cytoplasm to the nucleus and increases expression of many AHR-target genes such as *Cyp1a1* and *Cyp1b1* (REF.[109]). Bacteria metabolize dietary tryptophan to indole, which can be further modified by host enzymes in the liver into the AHR agonist indoxyl-3-sulfate (I3S)[109]. I3S then crosses the blood–brain barrier and has an immunosuppressive role through increasing AHR activities in both astrocytes[86] and microglia[110]. Under inflammatory conditions, such as EAE in mice and multiple sclerosis in humans, astrocytes upregulate AHR expression in response to type I interferon signalling and deletion of AHR in astrocytes exacerbates EAE phenotypes[86]. Mice fed a tryptophan-depleted diet or treated with antibiotic ampicillin exhibit exacerbated EAE symptoms, whereas supplementing their diet with indole or administrating I3S (a tryptophan microbial metabolite and

Aryl hydrocarbon receptor
(AHR). A cytosolic, ligand-dependent transcription factor that translocates to the nucleus following the binding of specific ligands, which include dietary and microbial metabolites. AHR participates in the differentiation of regulatory T cells, T helper 17 ($T_H17$) cells and intraepithelial intestinal γδ T cells, and is required for the secretion of IL-22 by $T_H17$ cells. More recently, AHR has been shown to have crucial roles in the development and function of lymphoid tissue inducer cells and group 3 innate lymphoid cells.

Astrocytes
The most abundant type of cell in the brain, named for their characteristic star-like shape. These cells provide both mechanical and metabolic support for neurons, such as supporting the formation and pruning of neuronal synapses.

Basolateral amygdala
A brain region extensively studied for its role in fear learning.

Segmented filamentous bacteria
A Gram-positive, spore-forming, non-culturable, Clostridia-related bacterium (provisionally named *Candidatus savagella* (of the Clostridiaceae family)) that resides in the terminal ileum in direct contact with intestinal epithelial cells and that induces the expression of IL-17A, IL-22 and IgA in the host.

AHR agonist) reduces EAE scores[86]. On the other hand, upon exposure to I3S, microglia express AHR that promotes expression of transforming growth factor-α (TGFα) but suppresses expression of vascular endothelial growth factor B (VEGFB), both of which act on astrocytes to limit or promote their function during the course of EAE, respectively[110]. Importantly, tryptophan or I3S administration to mice fed a tryptophan-depleted diet mitigated EAE symptoms in control mice, but not in mice lacking microglial expression of AHR, suggesting that AHR expression by microglia is necessary to mediate the immunosuppressive effects of tryptophan-derived bacterial metabolites on CNS-resident cells[110]. These findings define an AHR-mediated gut–brain axis by which bacterial metabolites from the gut control the inflammatory activities of CNS-resident cells.

***Immune cell-derived cytokines and the brain.*** Gut-residing bacteria likely use peripheral immune cells as intermediaries to communicate with cells in the brains. As described above, both bacteria and the small molecules they produce are known to promote differentiation of various types of immune cells. These immune cells in the periphery then produce soluble factors, mainly cytokines, to transmit information to the CNS. Indeed, neuronal and non-neuronal cells in the brain express multiple receptors for soluble factors that are often produced by immune cells in the periphery. The physiological functions of these receptors have not been systematically examined. Yet cytokines have extensive roles in the context of brain development, tissue damage and neuroinflammatory conditions (as reviewed elsewhere[111]). In addition, a growing number of studies have started to elucidate the underappreciated roles of cytokines in controlling synapse formation, neural functions and animal behaviours. For example, IL-18 and its receptor are expressed by neurons of the basolateral amygdala and modulate stress-induced depression[112]. TNF contributes to activity-dependent regulation of synaptic connectivity[113]. IL-1β negatively regulates neurogenesis and enhances memory impairment following West Nile virus infection[114]. Furthermore, cytokines mainly produced by T cells and other immune cells in the periphery also affect neural activities and animal behaviours. Interferon-γ (IFNγ), an inflammatory cytokine produced by $T_H1$ cells, acts in the hippocampus to reduce GABAergic inhibition, leading to network hyperexcitability[115]. Conversely, IFNγ acts on neurons in the prefrontal cortex to increase inhibitory GABAergic tone, which affects social behaviour in mice[116]. In experiments using a Morris water maze task to assess spatial learning and memory, the $T_H2$ cell-derived cytokine IL-4 was shown to be crucial for promoting learning and memory. Accordingly, germline depletion of *Il4* led to poorer performance in the cognitive tasks[117]. Similarly, IL-13 was shown to be essential for cognitive brain functions, as knockout of *Il13* led to impaired working memory. Furthermore, increased numbers of $CD4^+$ T cells are found in the meninges of mice trained in the Morris water maze in an IL-13-dependent or IL-4-dependent manner, which suggests that learning may mobilize T cells from the periphery to the brain or may induce their local proliferation in the brain[118]. Intriguingly, an orthologue of IL-17 encoded by *Caenorhabditis elegans*, *ilc-17.1*, as well as its receptor orthologues *ilcr-1* and *ilcr-2*, acts directly on neurons, modulating neuronal activity and social behavioural output in *C. elegans*[119]. Furthermore, IL-17A produced by meningeal γδ T cells was recently shown to be indispensable for promoting short-term, but not long-term, memory in mice[120], supporting a neuromodulatory role for this cytokine.

***Peripheral immune cells in the brain.*** In addition to sending signals to the brain by secreting cytokines, immune cells (thought to mainly exist in peripheral tissues) are also found in the brain. For example, IFNγ-producing T cells are highly enriched in the subventricular zone in the brains of old, but not young, mice and suppress proliferation of neural stem cells[121]. In the context of stroke, $T_{reg}$ cells accumulate in the mouse brain, accelerating neurological recovery[122].

Do commensal bacteria in the intestine contribute to the translocation of peripheral immune cells to the brain? More studies are needed to address this question, but intricate relationships exist between immunological events in the brain and changes in the bacterial communities in the intestine. Both traumatic spinal cord injury and acute brain ischaemia promote gut dysbiosis[123,124]. Antibiotic treatments leading to gut dysbiosis result in exacerbated disease phenotypes following spinal cord injury[123,124], whereas faecal microbiota transplantation reduces brain lesion size, mitigating stroke-induced phenotypes[124]. Previous studies showed that germ-free mice are resistant to EAE, but colonization of germ-free mice with segmented filamentous bacteria that promote $T_H17$ cell differentiation enhances EAE phenotypes[125]. By contrast, the commensal microorganism *Bacteroides fragilis* suppresses EAE symptoms when used to colonize mice raised under specific pathogen-free conditions[126]. These data suggest that changes in gut bacteria community may contribute to CNS disease phenotypes, perhaps by relying on peripheral immune cells as messengers.

There are a few recent examples showing that immune cells in the gut translocate to the brain. Whereas IL-17A-producing γδ T cells promote brain ischaemia injury, IL-10-producing $T_{reg}$ cells protect against post-ischaemic brain damage[127,128]. Two groups independently performed elegant in vivo cell tracking studies to demonstrate that gut-residing γδ T cells translocate into the brain meninges following a stroke[124,129]. Increased levels of peripherally derived γδ T cells that secrete IL-17A were also found in the epileptogenic lesions of both human patients and mouse epileptic models, where their cell numbers in the CNS correlate with disease severity[130]. IL-17RA-deficient mice display a significantly delayed onset of seizures, suggesting a causative role of the IL-17A–IL-17RA pathway in exacerbating seizures[130].

During EAE, IgA-producing plasma cells, which develop in the gut in response to commensal bacteria, are detected in the CNS. Removal of both plasmablasts and plasma cells exacerbates EAE[90]. Rotavirus-specific IgA-producing plasmablasts and plasma cells, generated

in response to rotavirus infection of mature enterocytes in the small intestine, can be recruited to other tissues, such as the bone marrow and lungs, upon infection with influenza virus. Furthermore, rotavirus-specific IgA-producing cells can also be found in the CNS during peak and chronic EAE[90]. Lastly, IgA-producing plasmablasts and plasma cells suppress EAE phenotypes in an IL-10-dependent manner.

Together, these studies suggest that the gut–brain (or the gut–immune system–brain) axis can be harnessed to treat various neuroinflammatory and neuropathological diseases. Further studies are needed to understand how signals are initiated, propagated and transferred from the gut to the brain both at steady state and under pathophysiological conditions.

## The maternal gut–fetal brain axis

The gut–brain axis may also contribute to animal development during pregnancy. However, only a small number of studies have presented convincing results on the importance of this intergenerational gut–brain axis. Studies suggest that bacteria in the maternal gut regulate maternal immune cells to produce effector molecules. These effector molecules then serve as intermediaries and impact fetal brain development. Further evidence comes from studies using mice fed high-fat diets that presumably induce changes in the community of gut bacteria and immune cell function of pregnant mice. The offspring of pregnant mice fed high-fat diets exhibited alterations, such as social deficits and reduced levels of the neuromodulator oxytocin in the ventral tegmental area[108]. Importantly, both behavioural abnormalities and decreased oxytocin production in the brain were restored with the administration of *L. reuteri*[108], suggesting that the maternal gut–fetal brain axis can also impact the gut–brain axis of the affected offspring.

Importantly, pregnancy induces changes in the composition of gut-residing bacteria[131]. Recent studies have also shown that, during pregnancy, bacteria and immune cells in the maternal gut support fetal brain development. Notably, inducing gut dysbiosis in late pregnancy with a low dose of antibiotics results in long-term behavioural effects, including reduced sociability, in the offspring of mice[132]. Lack of maternal microbiota during pregnancy was recently shown to severely affect proper development of embryonic microglia of male, but not female, offspring[133]. Whereas more than 1,200 genes were differentially expressed between male microglia from specific pathogen-free versus germ-free embryos collected at embryonic day 18.5, only 20 genes were differentially expressed between female microglia isolated at the same time point[133]. Unexpectedly, these gender dimorphic effects on the differential gene expression between specific pathogen-free and germ-free conditions are reversed in adults, with more than 400 genes differentially regulated in female microglia whereas just 26 genes were downregulated in males.

One difficulty in using germ-free mice to study the effects of maternal microbiota on fetal brain development is uncoupling the roles of bacteria during pregnancy versus their effects after birth until weaning. The triple-mutant *Escherichia coli* strain HA107 has been elegantly used to generate a reversible germ-free colonization system in mice[134]. After colonizing germ-free mice with HA107, within 72 h the mice return to a germ-free state. Using this system, it was shown that gestational colonization of maternal microbiota not only contributes to the development of ILC3s but also promotes the transfer of bacteria-derived metabolites, including various ligands for AHR, into the fetal compartments[135,136].

Exposure to increased levels of maternal immune activation (MIA) during pregnancy can lead to brain pathologies and long-term behavioural changes in the affected offspring. In mouse models of MIA, adult offspring born of pregnant mice that were either exposed to viral infection or injected with a synthetic double-stranded RNA (poly(I:C)) mimicking viral infection exhibited behavioural abnormalities, such as abnormal communication, reduced sociability, repetitive behaviours and increased anxiety levels, which are reminiscent of core symptoms observed in human patients with neurodevelopmental disorders[137,138]. Using genetic mutants and blocking antibodies targeting $T_H17$ cells, it was shown that $T_H17$ cells contribute to the behavioural abnormalities in MIA-affected offspring[139]. Offspring are protected from the induction of MIA-dependent behavioural phenotypes when mothers are deficient in $T_H17$ cells or lack IL-17 activity. Similarly, offspring with a CNS-specific deficiency of IL-17RA, the expression of which is upregulated in the cortex of fetuses exposed to MIA, were also protected from MIA phenotypes[139,140]. Lastly, MIA phenotypes in offspring require maternal intestinal bacteria that promote $T_H17$ cell differentiation[88,89]. Pregnant mice were more likely to produce offspring with MIA-associated abnormalities if they had been colonized with mouse commensal segmented filamentous bacteria or human commensal bacteria that induce intestinal $T_H17$ cell development. Thus, pregnant mothers with defined gut commensal bacteria that promote $T_H17$ cell responses may have increased risk of neurodevelopmental disorders developing in their offspring if the mothers are exposed to infections or autoinflammatory syndromes[88,89].

## Concluding remarks

The immune and nervous systems have evolved to sense intrinsic and extrinsic stimuli to mount complex responses that contribute to health and survival of the host. Immune cells circulate through the body and can translocate to places where sensing and responding to the stimuli are needed to restore tissue homeostasis. In turn, neuronal cells, although stationary, can receive and relay information from and to immune cells at a distance using a well-organized circuitry. An intimate relationship between these two systems is emerging and has already provided many insights into neuroimmune circuits in health and disease. Neuroimmune cell units have been identified in multiple organs, where distinct neuronal and immune cell populations interact to modulate various physiological processes. As such, it is possible that, throughout evolution, coordinated neuroimmune interactions have been selected and preserved to ensure efficient responses to environmental challenges while preserving tissue homeostasis.

The more detailed understanding of neuroimmune interactions is generating new directions of study that will require novel interdisciplinary approaches. Traditional methods used to study neuronal activity in peripheral organs, including physical lesions, pharmacological and chemical inhibitors and electrical stimulation, provided the initial evidence that neuronal signals can impact immune responses. However, these methods are not sufficient to elucidate tissue-autonomous and cell-intrinsic mechanisms of neuroimmune cell interactions. Future use of combined tissue-specific optogenetics, chemogenetics and intercellular labelling systems may help to clarify the functional tenets of this bidirectional circuitry. Finally, another important challenge relates to the therapeutic potential of neuroimmune interactions in the context of immune and neuronal disorders. Pharmacological and bioelectronic approaches of vagus nerve stimulation have been tested for modulation of the inflammatory reflex[8], showing potential therapeutic benefit. For example, electric stimulation of the sciatic nerve leads to dopamine secretion in the adrenal medulla, suppressing systemic inflammation and increasing survival in sepsis[141]. But a more detailed understanding of peripheral neuroimmune circuits promises to reveal new therapeutic targets in the context of inflammatory, neurological, metabolic and oncogenic conditions.

Two-way or three-way (with bacteria) communications of immune cells with neurons take place throughout the body and in the brain. A comprehensive map of neuroimmune connections, or a 'connectome', needs to be constructed to understand how these communications work. To achieve this goal, concerted efforts need to be made: first, to identify a list of environmental factors that influence neuroimmune communications; second, to fully understand how immune cells and neurons interact in the periphery; and, third, to elucidate mechanisms by which immune molecules shape neural responses in the brain. Environmental factors include, but are not limited to, commensal bacteria, diet, infection and pollutants. Immune cells and neurons can interact with each other, perhaps by forming close physical interactions or by exchanging soluble factors through ligand–receptor interactions. Structural and functional identification of these interactions as well as elucidation of novel ligands (and their receptors) that mediate intercellular signalling cascades will help to fully characterize neuroimmune interactions. Many cytokine and chemokine receptors are expressed by both neuronal and non-neuronal cells in the brain. The question of how cytokines and chemokines act on these receptors and modulate brain circuit-level activity requires further investigation. A neuroimmune connectome will increase our understanding of how neuroimmune interactions come into play in response to both external and internal stimuli and will provide systems-level mechanistic insights into how brain function is affected by the immune system in disease and homeostatic states.

In conclusion, elucidating neuroimmune interactions promises to be a prominent field in biomedical research in the years to come. These efforts will have the potential to unravel novel and transformative biological underpinnings, which may be harnessed therapeutically in conditions such as cancer and inflammatory, neurological and metabolic diseases.

Published online 17 December 2019


1. Rankin, L. C. & Artis, D. Beyond host defense: emerging functions of the immune system in regulating complex tissue physiology. *Cell* **173**, 554–567 (2018).
2. Veiga-Fernandes, H. & Freitas, A. A. The s(c)ensory immune system theory. *Trends Immunol.* **38**, 777–788 (2017).
3. Besedovsky, H. et al. The immune response evokes changes in brain noradrenergic neurons. *Science* **221**, 564–566 (1983).
4. Stead, R. H. et al. Intestinal mucosal mast cells in normal and nematode-infected rat intestines are in intimate contact with peptidergic nerves. *Proc. Natl Acad. Sci. USA* **84**, 2975–2979 (1987).
5. Matsunaga, H. et al. Physiological stress exacerbates murine colitis by enhancing proinflammatory cytokine expression that is dependent on IL-18. *Am. J. Physiol. Gastrointest. Liver Physiol.* **301**, G555–G564 (2011).
6. Serrats, J. et al. Dual roles for perivascular macrophages in immune-to-brain signaling. *Neuron* **65**, 94–106 (2010).
7. Veiga-Fernandes, H. & Pachnis, V. Neuroimmune regulation during intestinal development and homeostasis. *Nat. Immunol.* **18**, 116–122 (2017).
8. Godinho-Silva, C., Cardoso, F. & Veiga-Fernandes, H. Neuro-immune cell units: a new paradigm in physiology. *Annu. Rev. Immunol.* **37**, 19–46 (2019).
9. Veiga-Fernandes, H. & Artis, D. Neuronal–immune system cross-talk in homeostasis. *Science* **359**, 1465–1466 (2018).
10. Veiga-Fernandes, H. & Mucida, D. Neuro-immune interactions at barrier surfaces. *Cell* **165**, 801–811 (2016).
11. Chesne, J., Cardoso, V. & Veiga-Fernandes, H. Neuro-immune regulation of mucosal physiology. *Mucosal Immunol.* **12**, 10–20 (2019).
12. Kabashima, K., Honda, T., Ginhoux, F. & Egawa, G. The immunological anatomy of the skin. *Nat. Rev. Immunol.* **19**, 19–30 (2019).
13. Oetjen, L. K. et al. Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. *Cell* **171**, 217–228 (2017).
14. Gupta, K. & Harvima, I. T. Mast cell–neural interactions contribute to pain and itch. *Immunol. Rev.* **282**, 168–187 (2018).
15. Serhan, N. et al. House dust mites activate nociceptor-mast cell clusters to drive type 2 skin inflammation. *Nat. Immunol.* **20**, 1435–1443 (2019).
16. Kolter, J. et al. A subset of skin macrophages contributes to the surveillance and regeneration of local nerves. *Immunity* **50**, 1482–1497 (2019).
17. Pinho-Ribeiro, F. A. et al. Blocking neuronal signaling to immune cells treats Streptococcal invasive infection. *Cell* **173**, 1083–1097 (2018).
18. Baral, P. et al. Nociceptor sensory neurons suppress neutrophil and γδ T cell responses in bacterial lung infections and lethal pneumonia. *Nat. Med.* **24**, 417–426 (2018).
**This study demonstrates that nociceptor neurons suppress immunity to bacterial lung infection via inhibition of neutrophil and γδ T cell recruitment.**
19. Kashem, S. W. et al. Nociceptive sensory fibers drive interleukin-23 production from CD301b$^{+}$ dermal dendritic cells and drive protective cutaneous immunity. *Immunity* **43**, 515–526 (2015).
20. Riol-Blanco, L. et al. Nociceptive sensory neurons drive interleukin-23-mediated psoriasiform skin inflammation. *Nature* **510**, 157–161 (2014).
21. Audrit, K. J., Delventhal, L., Aydin, O. & Nassenstein, C. The nervous system of airways and its remodeling in inflammatory lung diseases. *Cell Tissue Res.* **367**, 571–590 (2017).
22. Nassenstein, C., Kutschker, J., Tumes, D. & Braun, A. Neuro-immune interaction in allergic asthma: role of neurotrophins. *Biochem. Soc. Trans.* **34**, 591–593 (2006).
23. Chesne, J. et al. IL-17 in severe asthma. Where do we stand? *Am. J. Respir. Crit. Care Med.* **190**, 1094–1101 (2014).
24. Foster, S. L., Seehus, C. R., Woolf, C. J. & Talbot, S. Sense and immunity: context-dependent neuro-immune interplay. *Front. Immunol.* **8**, 1463 (2017).
25. Lee, L. Y. & Yu, J. Sensory nerves in lung and airways. *Compr. Physiol.* **4**, 287–324 (2014).
26. McGovern, A. E. & Mazzone, S. B. Neural regulation of inflammation in the airways and lungs. *Auton. Neurosci.* **182**, 95–101 (2014).
27. Costello, R. W. et al. Localization of eosinophils to airway nerves and effect on neuronal M2 muscarinic receptor function. *Am. J. Physiol.* **273**, L93–L103 (1997).
28. Nilsson, G., Alving, K., Ahlstedt, S., Hokfelt, T. & Lundberg, J. M. Peptidergic innervation of rat lymphoid tissue and lung: relation to mast cells and sensitivity to capsaicin and immunization. *Cell Tissue Res.* **262**, 125–133 (1990).
29. Jacoby, D. B., Costello, R. M. & Fryer, A. D. Eosinophil recruitment to the airway nerves. *J. Allergy Clin. Immunol.* **107**, 211–218 (2001).
30. Cyphert, J. M. et al. Cooperation between mast cells and neurons is essential for antigen-mediated bronchoconstriction. *J. Immunol.* **182**, 7430–7439 (2009).
31. Voisin, T., Bouvier, A. & Chiu, I. M. Neuro-immune interactions in allergic diseases: novel targets for therapeutics. *Int. Immunol.* **29**, 247–261 (2017).
32. Sawatzky, D. A. et al. Eosinophil adhesion to cholinergic nerves via ICAM-1 and VCAM-1 and associated eosinophil degranulation. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **282**, L1279–L1288 (2002).
33. Nie, Z., Nelson, C. S., Jacoby, D. B. & Fryer, A. D. Expression and regulation of intercellular adhesion molecule-1 on airway parasympathetic nerves. *J. Allergy Clin. Immunol.* **119**, 1415–1422 (2007).
34. Fryer, A. D. et al. Neuronal eotaxin and the effects of CCR3 antagonist on airway hyperreactivity and M2 receptor dysfunction. *J. Clin. Invest.* **116**, 228–236 (2006).

35. Ansel, J. C., Brown, J. R., Payan, D. G. & Brown, M. A. Substance P selectively activates TNF-α gene expression in murine mast cells. *J. Immunol.* **150**, 4478–4485 (1993).
36. Kulka, M., Sheen, C. H., Tancowny, B. P., Grammer, L. C. & Schleimer, R. P. Neuropeptides activate human mast cell degranulation and chemokine production. *Immunology* **123**, 398–410 (2008).
37. Nussbaum, J. C. et al. Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature* **502**, 245–248 (2013).
**This work demonstrates that VIP stimulates ILC2s, which in turn regulate eosinophil homeostasis.**
38. Talbot, S. et al. Silencing nociceptor neurons reduces allergic airway inflammation. *Neuron* **87**, 341–354 (2015).
**This study shows that nociceptor neurons are important regulators of pulmonary allergic reactions.**
39. Cardoso, V. et al. Neuronal regulation of type 2 innate lymphoid cells via neuromedin U. *Nature* **549**, 277–281 (2017).
40. Klose, C. S. N. et al. The neuropeptide neuromedin U stimulates innate lymphoid cells and type 2 inflammation. *Nature* **549**, 282–286 (2017).
41. Wallrapp, A. et al. The neuropeptide NMU amplifies ILC2-driven allergic lung inflammation. *Nature* **549**, 351–356 (2017).
**Together with references 39 and 40, this study shows that the neuronal-derived peptide NMU is a uniquely potent activator of ILC2s.**
42. Galle-Treger, L. et al. Nicotinic acetylcholine receptor agonist attenuates ILC2-dependent airway hyperreactivity. *Nat. Commun.* **7**, 13202 (2016).
43. Sui, P. et al. Pulmonary neuroendocrine cells amplify allergic asthma responses. *Science* **360**, eaan8546 (2018).
44. Barrios, J. et al. Early life allergen-induced mucus overproduction requires augmented neural stimulation of pulmonary neuroendocrine cell secretion. *FASEB J.* **31**, 4117–4128 (2017).
45. Nagashima, H. et al. Neuropeptide CGRP limits group 2 innate lymphoid cell responses and constrains type 2 inflammation. *Immunity* **51**, 682–695 (2019).
46. Wallrapp, A. et al. Calcitonin gene-related peptide negatively regulates alarmin-driven type 2 innate lymphoid cell responses. *Immunity* **51**, 709–723 (2019).
47. Xu, H. et al. Transcriptional atlas of intestinal immune cells reveals that neuropeptide α-CGRP modulates group 2 innate lymphoid cell responses. *Immunity* **51**, 696–708 (2019).
48. Assas, B. M., Pennock, J. I. & Miyan, J. A. Calcitonin gene-related peptide is a key neurotransmitter in the neuro-immune axis. *Front. Neurosci.* **8**, 23 (2014).
49. Veres, T. Z. et al. Spatial interactions between dendritic cells and sensory nerves in allergic airway inflammation. *Am. J. Respir. Cell Mol. Biol.* **37**, 553–561 (2007).
50. Veres, T. Z., Rochlitzer, S. & Braun, A. The role of neuro-immune cross-talk in the regulation of inflammation and remodelling in asthma. *Pharmacol. Ther.* **122**, 203–214 (2009).
51. Veres, T. Z. et al. Dendritic cell–nerve clusters are sites of T cell proliferation in allergic airway inflammation. *Am. J. Pathol.* **174**, 808–817 (2009).
52. Furness, J. B., Callaghan, B. P., Rivera, L. R. & Cho, H. J. The enteric nervous system and gastrointestinal innervation: integrated local and central control. *Adv. Exp. Med. Biol.* **817**, 39–71 (2014).
53. Furness, J. B. Types of neurons in the enteric nervous system. *J. Auton. Nerv. Syst.* **81**, 87–96 (2000).
54. Matteoli, G. et al. A distinct vagal anti-inflammatory pathway modulates intestinal muscularis resident macrophages independent of the spleen. *Gut* **63**, 938–948 (2014).
55. Yoo, B. B. & Mazmanian, S. K. The enteric network: interactions between the immune and nervous systems of the gut. *Immunity* **46**, 910–926 (2017).
56. Kioussis, D. & Pachnis, V. Immune and nervous systems: more than just a superficial similarity? *Immunity* **31**, 705–710 (2009).
57. van Diest, S. A., Stanisor, O. I., Boeckxstaens, G. E., de Jonge, W. J. & van den Wijngaard, R. M. Relevance of mast cell–nerve interactions in intestinal nociception. *Biochim. Biophys. Acta* **1822**, 74–84 (2012).
58. Stead, R. H., Dixon, M. F., Bramwell, N. H., Riddell, R. H. & Bienenstock, J. Mast cells are closely apposed to nerves in the human gastrointestinal mucosa. *Gastroenterology* **97**, 575–585 (1989).
59. Tamura, K. & Wood, J. D. Effects of prolonged exposure to histamine on guinea pig intestinal neurons. *Dig. Dis. Sci.* **37**, 1084–1088 (1992).
60. Reed, D. E. et al. Mast cell tryptase and proteinase-activated receptor 2 induce hyperexcitability of guinea-pig submucosal neurons. *J. Physiol.* **547**, 531–542 (2003).
61. Steinhoff, M. et al. Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. *Nat. Med.* **6**, 151–158 (2000).
62. Shanahan, F., Denburg, J. A., Fox, J., Bienenstock, J. & Befus, D. Mast cell heterogeneity: effects of neuroenteric peptides on histamine release. *J. Immunol.* **135**, 1331–1337 (1985).
63. Caughey, G. H., Leidig, F., Viro, N. F. & Nadel, J. A. Substance P and vasoactive intestinal peptide degradation by mast cell tryptase and chymase. *J. Pharmacol. Exp. Ther.* **244**, 133–137 (1988).
64. Barbara, G. et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology* **126**, 693–702 (2004).
65. Barbara, G. et al. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. *Gastroenterology* **132**, 26–37 (2007).
66. Buhner, S. et al. Activation of human enteric neurons by supernatants of colonic biopsy specimens from patients with irritable bowel syndrome. *Gastroenterology* **137**, 1425–1434 (2009).
67. Belai, A., Boulos, P. B., Robson, T. & Burnstock, G. Neurochemical coding in the small intestine of patients with Crohn's disease. *Gut* **40**, 767–774 (1997).
68. Bai, A., Lu, N., Guo, Y., Chen, J. & Liu, Z. Modulation of inflammatory response via α2-adrenoceptor blockade in acute murine colitis. *Clin. Exp. Immunol.* **156**, 353–362 (2009).
69. Xia, C. M., Colomb, D. G. Jr., Akbarali, H. I. & Qiao, L. Y. Prolonged sympathetic innervation of sensory neurons in rat thoracolumbar dorsal root ganglia during chronic colitis. *Neurogastroenterol. Motil.* **23**, 801-e339 (2011).
70. Bain, C. C. & Mowat, A. M. Macrophages in intestinal homeostasis and inflammation. *Immunol. Rev.* **260**, 102–117 (2014).
71. Gabanyi, I. et al. Neuro-immune interactions drive tissue programming in intestinal macrophages. *Cell* **164**, 378–391 (2016).
72. Muller, P. A. et al. Crosstalk between muscularis macrophages and enteric neurons regulates gastrointestinal motility. *Cell* **158**, 300–313 (2014).
**This study shows that macrophages and neurons in the intestinal muscularis interact in a bidirectional manner.**
73. Pirzgalska, R. M. et al. Sympathetic neuron-associated macrophages contribute to obesity by importing and metabolizing norepinephrine. *Nat. Med.* **23**, 1309–1318 (2017).
74. Klose, C. S. & Artis, D. Innate lymphoid cells as regulators of immunity, inflammation and tissue homeostasis. *Nat. Immunol.* **17**, 765–774 (2016).
75. Ibiza, S. et al. Glial-cell-derived neuroregulators control type 3 innate lymphoid cells and gut defence. *Nature* **535**, 440–443 (2016).
**This study indicates that intestinal ILC3s can integrate neuroglia-derived factors.**
76. Veiga-Fernandes, H. et al. Tyrosine kinase receptor RET is a key regulator of Peyer's patch organogenesis. *Nature* **446**, 547–551 (2007).
77. Patel, A. et al. Differential RET signaling pathways drive development of the enteric lymphoid and nervous systems. *Sci. Signal.* **5**, ra55 (2012).
78. Fonseca-Pereira, D. et al. The neurotrophic factor receptor RET drives haematopoietic stem cell survival and function. *Nature* **514**, 98–101 (2014).
79. Dalli, J., Colas, R. A., Arnardottir, H. & Serhan, C. N. Vagal regulation of group 3 innate lymphoid cells and the immunoresolvent PCTR1 controls infection resolution. *Immunity* **46**, 92–105 (2017).
80. Godinho-Silva, C. et al. Light-entrained and brain-tuned circadian circuits regulate ILC3s and gut homeostasis. *Nature* **574**, 254–258 (2019).
**This study shows that photonic cues and brain-derived circadian signals are major regulators of intestinal ILC3 homeostasis.**
81. Wang, Q. et al. Circadian rhythm-dependent and circadian rhythm-independent impacts of the molecular clock on type 3 innate lymphoid cells. *Sci. Immunol.* **4**, eaay7501 (2019).
82. Teng, F. et al. A circadian clock is essential for homeostasis of group 3 innate lymphoid cells in the gut. *Sci. Immunol.* **4**, eaax1215 (2019).
83. Moriyama, S. et al. β2-Adrenergic receptor-mediated negative regulation of group 2 innate lymphoid cell responses. *Science* **359**, 1056–1061 (2018).
84. Scott, K. A. et al. Revisiting Metchnikoff: age-related alterations in microbiota–gut–brain axis in the mouse. *Brain Behav. Immun.* **65**, 20–32 (2017).
85. Sgritta, M. et al. Mechanisms underlying microbial-mediated changes in social behavior in mouse models of autism spectrum disorder. *Neuron* **101**, 246–259 (2019).
**This study reports that gut-residing bacteria affect animal behaviour by stimulating the production of the neuromodulator oxytocin in the brain.**
86. Rothhammer, V. et al. Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. *Nat. Med.* **22**, 586–597 (2016).
87. Erny, D. et al. Host microbiota constantly control maturation and function of microglia in the CNS. *Nat. Neurosci.* **18**, 965–977 (2015).
**This study shows that gut bacteria contribute to the proper development of microglia.**
88. Kim, S. et al. Maternal gut bacteria promote neurodevelopmental abnormalities in mouse offspring. *Nature* **549**, 528–532 (2017).
89. Lammert, C. R. et al. Cutting edge: critical roles for microbiota-mediated regulation of the immune system in a prenatal immune activation model of autism. *J. Immunol.* **201**, 845–850 (2018).
**Together with reference 88, this study illustrates the critical function of gut bacteria in pregnant dams in promoting neurodevelopmental disorder-like phenotypes in their offspring.**
90. Rojas, O. L. et al. Recirculating intestinal IgA-producing cells regulate neuroinflammation via IL-10. *Cell* **176**, 610–624 (2019).
**This study shows that IgA-producing B cells can migrate from the gut to the brain.**
91. Haghikia, A. et al. Dietary fatty acids directly impact central nervous system autoimmunity via the small intestine. *Immunity* **43**, 817–829 (2015).
92. Smith, P. M. et al. The microbial metabolites, short-chain fatty acids, regulate colonic $T_{reg}$ cell homeostasis. *Science* **341**, 569–573 (2013).
93. Arpaia, N. et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* **504**, 451–455 (2013).
94. Furusawa, Y. et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* **504**, 446–450 (2013).
95. Kleinewietfeld, M. et al. Sodium chloride drives autoimmune disease by the induction of pathogenic $T_H17$ cells. *Nature* **496**, 518–522 (2013).
96. Wu, C. et al. Induction of pathogenic $T_H17$ cells by inducible salt-sensing kinase SGK1. *Nature* **496**, 513–517 (2013).
97. Wilck, N. et al. Salt-responsive gut commensal modulates $T_H17$ axis and disease. *Nature* **551**, 585–589 (2017).
98. Smits, H. H. et al. Selective probiotic bacteria induce IL-10-producing regulatory T cells in vitro by modulating dendritic cell function through dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin. *J. Allergy Clin. Immunol.* **115**, 1260–1267 (2005).
99. Cervantes-Barragan, L. et al. *Lactobacillus reuteri* induces gut intraepithelial $CD4^+CD8\alpha\alpha^+$ T cells. *Science* **357**, 806–810 (2017).
100. Sujino, T. et al. Tissue adaptation of regulatory and intraepithelial $CD4^+$ T cells controls gut inflammation. *Science* **352**, 1581–1586 (2016).
101. Kadowaki, A. et al. Gut environment-induced intraepithelial autoreactive $CD4^+$ T cells suppress central nervous system autoimmunity via LAG-3. *Nat. Commun.* **7**, 11639 (2016).
102. Zelante, T. et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. *Immunity* **39**, 372–385 (2013).
103. Faraco, G. et al. Dietary salt promotes neurovascular and cognitive dysfunction through a gut-initiated $T_H17$ response. *Nat. Neurosci.* **21**, 240–249 (2018).
104. Tabouy, L. et al. Dysbiosis of microbiome and probiotic treatment in a genetic model of autism spectrum disorders. *Brain Behav. Immun.* **73**, 310–319 (2018).
105. Bravo, J. A. et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc. Natl Acad. Sci. USA* **108**, 16050–16055 (2011).

106. Marin, I. A. et al. Microbiota alteration is associated with the development of stress-induced despair behavior. *Sci. Rep.* **7**, 43859 (2017).
107. Poutahidis, T. et al. Microbial symbionts accelerate wound healing via the neuropeptide hormone oxytocin. *PLOS ONE* **8**, e78898 (2013).
108. Buffington, S. A. et al. Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. *Cell* **165**, 1762–1775 (2016).
109. Rothhammer, V. & Quintana, F. J. The aryl hydrocarbon receptor: an environmental sensor integrating immune responses in health and disease. *Nat. Rev. Immunol.* **19**, 184–197 (2019).
110. Rothhammer, V. et al. Microglial control of astrocytes in response to microbial metabolites. *Nature* **557**, 724–728 (2018).
111. Becher, B., Spath, S. & Goverman, J. Cytokine networks in neuroinflammation. *Nat. Rev. Immunol.* **17**, 49–59 (2017).
112. Kim, T. K. et al. Local interleukin-18 system in the basolateral amygdala regulates susceptibility to chronic stress. *Mol. Neurobiol.* **54**, 5347–5358 (2017).
113. Stellwagen, D. & Malenka, R. C. Synaptic scaling mediated by glial TNF-α. *Nature* **440**, 1054–1059 (2006).
114. Garber, C. et al. Astrocytes decrease adult neurogenesis during virus-induced memory dysfunction via IL-1. *Nat. Immunol.* **19**, 151–161 (2018).
115. Zhu, P. J. et al. Suppression of PKR promotes network excitability and enhanced cognition by interferon-γ-mediated disinhibition. *Cell* **147**, 1384–1396 (2011).
116. Filiano, A. J. et al. Unexpected role of interferon-γ in regulating neuronal connectivity and social behaviour. *Nature* **535**, 425–429 (2016).
117. Derecki, N. C. et al. Regulation of learning and memory by meningeal immunity: a key role for IL-4. *J. Exp. Med.* **207**, 1067–1080 (2010).
118. Brombacher, T. M. et al. IL-13-mediated regulation of learning and memory. *J. Immunol.* **198**, 2681–2688 (2017).
119. Chen, C. et al. IL-17 is a neuromodulator of *Caenorhabditis elegans* sensory responses. *Nature* **542**, 43–48 (2017).
**This study uses forward genetic approaches and demonstrates that IL-17 is a neuromodulator that affects animal behaviours.**
120. Ribeiro, M. et al. Meningeal γδ T cell-derived IL-17 controls synaptic plasticity and short-term memory. *Sci. Immunol.* **4**, eaay5199 (2019).
121. Dulken, B. W. et al. Single-cell analysis reveals T cell infiltration in old neurogenic niches. *Nature* **571**, 205–210 (2019).
122. Ito, M. et al. Brain regulatory T cells suppress astrogliosis and potentiate neurological recovery. *Nature* **565**, 246–250 (2019).
123. Kigerl, K. A. et al. Gut dysbiosis impairs recovery after spinal cord injury. *J. Exp. Med.* **213**, 2603–2620 (2016).
124. Singh, V. et al. Microbiota dysbiosis controls the neuroinflammatory response after stroke. *J. Neurosci.* **36**, 7428–7440 (2016).
**This study demonstrates that the microbiota can determine inflammatory outcomes after stroke.**
125. Lee, Y. K., Menezes, J. S., Umesaki, Y. & Mazmanian, S. K. Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis. *Proc. Natl Acad. Sci. USA* **108**, 4615–4622 (2011).
126. Ochoa-Reparaz, J. et al. Central nervous system demyelinating disease protection by the human commensal *Bacteroides fragilis* depends on polysaccharide A expression. *J. Immunol.* **185**, 4101–4108 (2010).
127. Liesz, A. et al. Regulatory T cells are key cerebroprotective immunomodulators in acute experimental stroke. *Nat. Med.* **15**, 192–199 (2009).
128. Shichita, T. et al. Pivotal role of cerebral interleukin-17-producing γδT cells in the delayed phase of ischemic brain injury. *Nat. Med.* **15**, 946–950 (2009).
129. Benakis, C. et al. Commensal microbiota affects ischemic stroke outcome by regulating intestinal γδ T cells. *Nat. Med.* **22**, 516–523 (2016).
**This study shows that gut-residing γδ T cells can migrate into the brain**.
130. Xu, D. et al. Peripherally derived T regulatory and γδ T cells have opposing roles in the pathogenesis of intractable pediatric epilepsy. *J. Exp. Med.* **215**, 1169–1186 (2018).
131. Koren, O. et al. Host remodeling of the gut microbiome and metabolic changes during pregnancy. *Cell* **150**, 470–480 (2012).
**This study reports that pregnancy alone can induce changes in the gut microbial community of a pregnant female.**
132. Leclercq, S. et al. Low-dose penicillin in early life induces long-term changes in murine gut microbiota, brain cytokines and behavior. *Nat. Commun.* **8**, 15062 (2017).
133. Thion, M. S. et al. Microbiome influences prenatal and adult microglia in a sex-specific manner. *Cell* **172**, 500–516 (2018).
134. Hapfelmeier, S. et al. Reversible microbial colonization of germ-free mice reveals the dynamics of IgA immune responses. *Science* **328**, 1705–1709 (2010).
135. Gomez de Aguero, M. et al. The maternal microbiota drives early postnatal innate immune development. *Science* **351**, 1296–1302 (2016).
136. Smith, K., McCoy, K. D. & Macpherson, A. J. Use of axenic animals in studying the adaptation of mammals to their commensal intestinal microbiota. *Semin. Immunol.* **19**, 59–69 (2007).
137. Shi, L., Fatemi, S. H., Sidwell, R. W. & Patterson, P. H. Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. *J. Neurosci.* **23**, 297–302 (2003).
138. Malkova, N. V., Yu, C. Z., Hsiao, E. Y., Moore, M. J. & Patterson, P. H. Maternal immune activation yields offspring displaying mouse versions of the three core symptoms of autism. *Brain Behav. Immun.* **26**, 607–616 (2012).
139. Choi, G. B. et al. The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. *Science* **351**, 933–939 (2016).
140. Shin Yim, Y. et al. Reversing behavioural abnormalities in mice exposed to maternal inflammation. *Nature* **549**, 482–487 (2017).
141. Torres-Rosas, R. et al. Dopamine mediates vagal modulation of the immune system by electroacupuncture. *Nat. Med.* **20**, 291–295 (2014).



**Acknowledgements**
This work was supported by the Simons Foundation Autism Research Initiative (J.R.H.), the Jeongho Kim Neurodevelopmental Research Fund (J.R.H.), the Pew Scholar for Biomedical Sciences (J.R.H.), the US National Institutes of Health (grant R01MH119459) (J.R.H), the European Research Council (647274) (H.V.-F.), the Fundação para a Ciência e Tecnologia Portugal (H.V.-F.) and the Paul G. Allen Frontiers Group (H.V.-F.).


**Author contributions**
J.R.H. and H.V.-F. both wrote and edited the manuscript.

**Competing interests**
The authors declare no competing interests.

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